J|A|C|S
ARTICLES
Published on Web 03/13/2004

Total Synthesis of the Ristocetin Aglycon

Brendan M. Crowley, Yoshiki Mori, Casey C. McComas, Datong Tang, and Dale L. Boger*

Contribution from the Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037

Received November 25, 2003; E-mail: boger@scripps.edu

Abstract: The first total synthesis of the ristocetin aglycon is described employing a modular and highly convergent strategy. An effective 12-step (12% overall) synthesis of the ABCD ring system **3** from its amino acid subunits sequentially features an intramolecular aromatic nucleophilic substitution reaction for formation of the diaryl ether and closure of the 16-membered CD ring system (65%), a respectively diastereoselective (3:1, 86%) Suzuki coupling for installation of the AB biaryl linkage on which the atropisomer stereochemistry can be further thermally adjusted, and an effective macrolactamization (51%) for closure of the 12-membered AB ring system. A similarly effective 13-step (14% overall) synthesis of the 14-membered EFG ring system **4** was implemented employing a room-temperature intermolecular S_NAr reaction of an *o*-fluoronitroaromatic for formation of the FG diaryl ether (69%) and a key macrolactamization (92%) with formation of the amide linking residues 1 and 2. The two key fragments **3** and **4** were coupled, and the remaining 16-membered DE ring system was closed via diaryl ether formation to provide the ristocetin tetracyclic ring system (15 steps, 8% overall) enlisting an unusually facile (25 °C, 8 h, DMF, ≥95%) and diastereoselective (≥15:1) aromatic nucleophilic substitution reaction that benefits from substrate preorganization.

Ristocetin A[1,2] (**1**, Figure 1) was discovered alongside vancomycin,[3−6] the drug of last resort for treating resistant bacterial infections,[7] in the early 1950s and exhibits similar antibiotic activity.[1] Isolated from *Nocardia lurida*[8] and patented for use as an antibacterial by Abbott in 1961,[9] ristocetin A was discontinued in clinical use 2 years after being introduced due to incidences of patient mortality[10] attributable to platelet aggregation.[11] Subsequently, this latter activity was found to be eliminated through enzymatic cleavage of rhamnose from the pendant tetrasaccharide.[12] Currently, ristocetin A is used clinically to diagnose von Willebrand's disease, a common genetic hemorrhagic disorder[11] and has found use as an electrophoretic and chromatographic chiral selector.[13] The natural product aglycon **2** has been established to be slightly more active than its parent as well as free of the platelet aggregation activity.[14] Consequently, **2** and its semisynthetic derivatives have emerged as useful entry points for the discovery of new antibiotics that exhibit activity against vancomycin-resistant bacteria.[15,16]

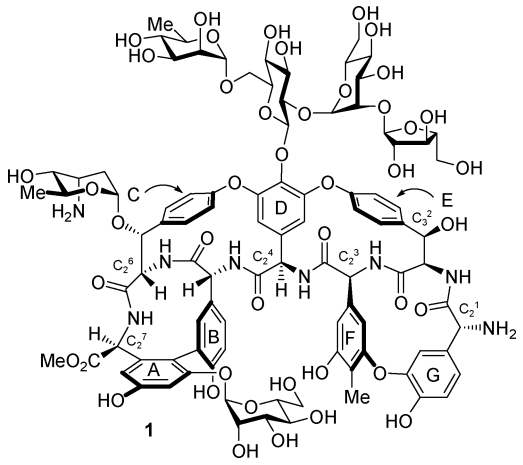


Figure 1. Ristocetin A.

(1) Isolation: Philip, J. E.; Schenck, J. R.; Hargie, M. P. *Antibiot. Annu*. **1956**−**57**, 699. Grundy, W. E.; Sinclair, A. C.; Theriault, R. J.; Goldstein, A. W.; Rickher, C. J.; Warren, H. B., Jr.; Oliver, T. J., Sylvester, J. C. *Antibiot. Annu*. **1956**−**57**, 687.
(2) Structure: Fehlner, J. R.; Hutchinson, R. E. J.; Tarbell, D. S.; Schenck, J. R. *Proc. Natl. Acad. Sci. U.S.A.* **1972**, *69*, 2420. Williams, D. H.; Rajananda, V.; Bojesen, G.; Williamson, M. P. *J. Chem. Soc. Chem. Commun.* **1979**, *20*, 906. Kalman, J. R.; Williams, D. H. *J. Am. Chem. Soc.* **1980**, *102*, 897. Williamson, M. P.; Williams, D. H. *Tetrahedron Lett.* **1980**, *21*, 4187. Harris, C. M.; Harris, T. M. *J. Am. Chem. Soc.* **1982**, *104*, 363.
(3) Vancomycin, structure: Harris, C. M.; Kopecka, H.; Harris, T. M. *J. Am. Chem. Soc.* **1983**, *105*, 6915. Williamson, M. P.; Williams, D. H. *J. Am. Chem. Soc.* **1981**, *103*, 6580. Harris, C. M.; Harris, T. M. *J. Am. Chem. Soc.* **1982**, *104*, 4293. Sheldrick, G. M.; Jones, P. G.; Kennard, O.; Williams, D. H.; Smith, G. A. *Nature* **1978**, *271*, 223. Williams, D. H.; Kalman, J. R. *J. Am. Chem. Soc.* **1977**, *99*, 2768. Isolation: McCormick, M. H.; Stark, W. M.; Pittenger, G. E.; Pittenger, R. C.; McGuire, J. M. *Antibiot. Annu.* **1955**−**56**, 606.
(4) Malabarba, A.; Nicas, T. I.; Thompson, R. C. *Med. Res. Rev.* **1997**, *17*, 69.
(5) Williams, D. H.; Bardsley, B. *Angew. Chem., Int. Ed.* **1999**, *38*, 1172.
(6) Hubbard, B. K.; Walsh, C. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 730. Walsh, C. *Nature* **2000**, *406*, 775. Walsh, C. T.; Fisher, S. L.; Park, I.-S.; Prahalad, M.; Wu, Z. *Chem. Biol.* **1996**, *3*, 21.
(7) Wiedemann, B.; Grimm, H. In *Antibiotics in Laboratory Medicine*; Lorian, V., Ed.; Williams and Wilkins: Baltimore, MD, 1996; pp 900−1168.
(8) Later reclassified *Amycolatopsis orientalis*: Lechevalier, M. P.; Prauser, H.; Labeda, D. P.; Ruan, J.-S. *Int. J. Syst. Bacteriol.* **1986**, *36*, 29.
(9) Philip, J. E.; Schenck, J. R. U.S. Patent 2,990,329, 1961.
(10) Dries, C. P.; Koch, R. *J. Pediatr.* **1960**, *56*, 498. Herting, R. L.; Lees, B.; Zimmerman, A. J.; Berryman G. H. *J. Am. Med. Assoc.* **1959**, *170*, 176.
(11) Howard, M. A.; Firkin, B. G. *Thromb. Diath. Haemorrh.* **1971**, *26*, 362.
(12) Kuwahara, S.; Chambers, W. T. *Experientia* **1978**, *34*, 532.
(13) Ward, T. J.; Farris, A. B. *J. Chromatogr., A* **2001**, *906*, 73.
(14) Herrin, T. R.; Thomas, A. M. U.S. Patent 4,456,593, 1984; *Chem. Abstr.* **1984**, *101*, 210855.

10.1021/ja039795a CCC: $27.50

Herein we provide full details of the first total synthesis of the ristocetin aglycon (**2**).[17] The aglycon **2** differs from that of teicoplanin[18] in subtle ways and more significantly from that of vancomycin,[3] both of which have been the subject of recent synthetic efforts.[18−22] The ristocetin aglycon possesses the identical tetracyclic ring system of teicoplanin[18] but lacks the C and E ring aryl chlorides that are also characteristic of the vancomycin structure. This removes the element of atropisomer stereochemistry in the CD and DE ring systems, simplifying the synthetic challenge of their construction. Unlike teicoplanin, ristocetin incorporates an additional C_6^3 aryl methyl group on the F ring as well as a sensitive C_3^2 β-hydroxy group within the E subunit like that found in vancomycin. Like teicoplanin, ristocetin contains a 14-membered diaryl ether FG ring system not found in vancomycin, which incorporates a racemization prone phenylglycine residue (C_2^3), making it a more challenging synthetic target than vancomycin.

The approach to the ristocetin aglycon was based largely on our second generation total synthesis of the teicoplanin aglycon.[18] Thus, the aglycon was to be assembled in a highly convergent approach from **3** and **4** representing the intact ABCD ring system and the EFG subunit incorporating the preformed FG ring system, Figure 2. Coupling of **3** and **4** followed by DE ring closure by a nucleophilic aromatic substitution reaction of a phenoxide on an *o*-fluoronitroaromatic would not only introduce the diaryl ether linkage but also complete the assemblage of the ristocetin tetracyclic ring system. The key DE ring closure conducted at this stage was anticipated to benefit from an apparent preorganization of the substrate resulting in facile closure under conditions much milder than those required of vancomycin.[23] Offsetting this advantage is the propensity for C_2^3 epimerization under even mildly basic conditions which might preclude successful implementation of this approach. The alternatives include coupling the intact ABCD ring system with an immediate precursor to **4**, incorporating an acyclic FG intermediate. This less convergent approach requires late stage closure of the FG ring system but proceeds through intermediates less prone to C_2^3 epimerization and with a key DE ring closure that likely would be less facile. Consequently, it appeared to be an accessible alternative should difficulties have arisen with the more convergent first generation approach.

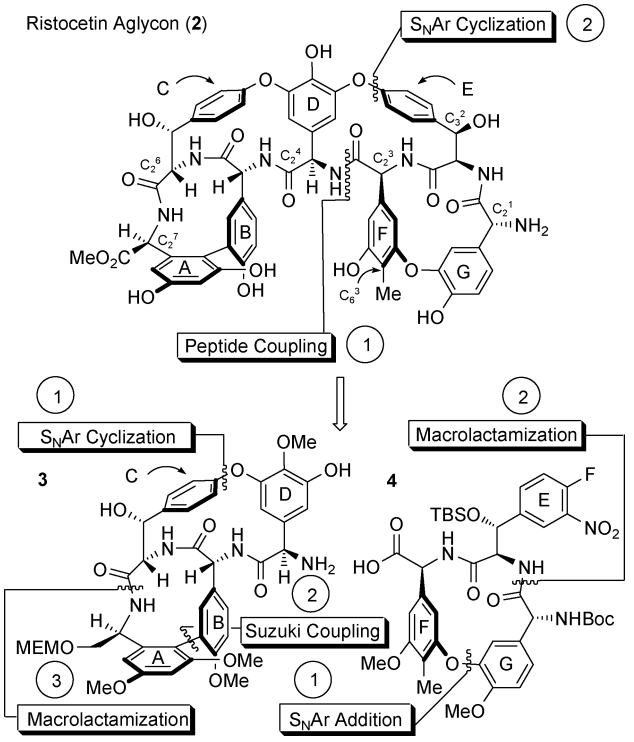


Figure 2. Key disconnections.

In turn, the ABCD ring system was anticipated to be available through sequential CD and AB ring closures analogous to our efforts on vancomycin. Notably, control of the CD atropisomer stereochemistry is not an issue with ristocetin by virtue of its lack of a C ring aryl chloride rendering the diastereoselectivity of a diaryl ether macrocyclization of an *o*-fluoronitroaromatic unimportant (activating NO_2 is removed). Thus, the stereochemical issues associated with this approach simplified to the control of the AB atropisomer stereochemistry. We felt this could be effectively addressed with an anticipated thermodynamic preference for the natural stereochemistry (ca. 3:1) most

(15) McComas, C. C.; Crowley, B. M.; Hwang, I.; Boger, D. L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2933.

(16) Ristocetin derivatives: Balzarini, J.; Pannecouque, C.; De Clercq, E.; Pavlov, A. Y.; Printsevskaya, S. S.; Miroshnikova, O. V.; Reznikova, M. I.; Preobrazhenskaya, M. N. *J. Med. Chem.* **2003**, *46*, 2755. Kobrin, M. B.; Katrukha, H. S.; Fedorova, G. B. *J. Antibiot.* **1989**, *42*, 1441. Barna, J. C. J.; Williams, D. H.; Williamson, M. P. *J. Chem. Soc., Chem. Commun.* **1985**, 254. Herrin, T. R.; Thomas, A. M.; Perun, T. J.; Mao, J. C.; Fesik, S. W. *J. Med. Chem*. **1985**, *28*, 1371.

(17) Aside from the efforts detailed herein, only Pearson has disclosed studies deliberately targeting ristocetin: Pearson, A. J.; Heo, J.-N. *Org. Lett.* **2000**, *2*, 2987. Pearson, A. J.; Zigmantas, S. *Tetrahedron Lett.* **2001**, *42*, 8765.

(18) Teicoplanin isolation: Parenti, F.; Beretta, G.; Berti, M.; Arioti, V. *J. Antibiot.* **1978**, *31*, 276. Structure: Hunt, A. H.; Molloy, R. M.; Occolowitz, J. L.; Marconi, G. G.; Debono, M. *J. Am. Chem. Soc.* **1984**, *106*, 4891. Barna, J. C. J.; Williams, D. H.; Stone, D. J. M.; Leung, T.-W. C.; Doddrell, D. M. *J. Am. Chem. Soc.* **1984**, *106*, 4895. Total synthesis: Boger, D. L.; Kim, S. H.; Miyazaki, S.; Strittmatter, H.; Weng, J.-H.; Mori, Y.; Rogel, O.; Castle, S. L.; McAtee, J. J. *J. Am. Chem. Soc.* **2000**, *122*, 7416. Boger, D. L.; Kim, S. H.; Miyazaki, S.; Mori, Y.; Weng, J.-H.; Rogel, O.; Castle, S. L.; McAtee, J. J. *J. Am. Chem. Soc.* **2001**, *123*, 1862. Evans, D. A.; Katz, J. L.; Peterson, G. S.; Hintermann, T. *J. Am. Chem. Soc.* **2001**, *123*, 12411. Teicoplanin atropisomerism: Boger, D. L.; Weng, J. H.; Miyazaki, S.; McAtee, J. J.; Castle, S. L.; Kim, S. H.; Mori, Y.; Rogel, O.; Jin, Q. *J. Am. Chem. Soc.* **2000**, *122*, 10047.

(19) Vancomycin aglycon: Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Loiseleur, O.; Castle, S. L. *J. Am. Chem. Soc*. **1999**, *121*, 3226. Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Castle, S. L.; Loiseleur, O.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 10004. Vancomycin atropisomerism: Boger, D. L.; Miyazaki, S.; Loiseleur, O.; Beresis, R. T.; Castle, S. L.; Wu, J. H.; Jin, Q. *J. Am. Chem. Soc.* **1998**, *120*, 8920. Boger, D. L.; Beresis, R. T.; Loiseleur, O.; Wu, J. H.; Castle, S. L. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 721. Boger, D. L.; Loiseleur, O.; Castle, S. L.; Beresis, R. T.; Wu, J. H. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 3199. Boger, D. L.; Castle, S. L.; Miyazaki, S.; Wu, J. H.; Beresis, R. T.; Loiseleur, O. *J. Org. Chem.* **1999**, *64*, 70.

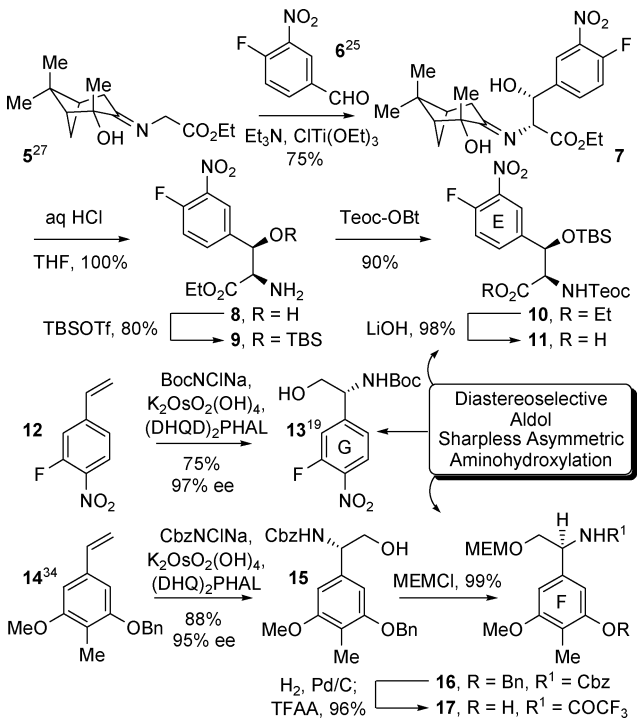
(20) Vancomycin: Nicolaou, K. C.; Li, H.; Boddy, C. N. C.; Ramanjulu, J. M.; Yue, T.-Y.; Natarajan, S.; Chu, X.-J.; Brase, S.; Rubsam, F. *Chem.—Eur. J.* **1999**, *5*, 2584. Nicolaou, K. C.; Boddy, C. N. C.; Li, H.; Koumbis, A. E.; Hughes, R.; Natarajan, S.; Jain, N. F.; Ramanjulu, J. M.; Brase, S.; Solomon, M. E. *Chem.—Eur. J*. **1999**, *5*, 2602. Nicolaou, K. C.; Koumbis, A. E.; Takayanagi, M.; Natarajan, S.; Jain, N. F.; Bando, T.; Li, H.; Hughes, R. *Chem.—Eur. J*. **1999**, *5*, 2622. Nicolaou, K. C.; Mitchell, H. J.; Jain, N. F.; Bando, T.; Hughes, R.; Winssinger, N.; Natarajan, S.; Koumbis, A. E. *Chem.—Eur. J*. **1999**, *5*, 2648.

(21) Orienticin C aglycon: Evans, D. A.; Barrow, J. C.; Watson, P. S.; Ratz, A. M.; Dinsmore, C. J.; Evrard, D. A.; DeVries, K. M.; Ellman, J. A.; Rychnovsky, S. D.; Lacour, J. *J. Am. Chem. Soc.* **1997**, *119*, 3419. Evans, D. A.; Dinsmore, C. J.; Ratz, A. M.; Evrard, D. A.; Barrow, J. C. *J. Am. Chem. Soc*. **1997**, *119*, 3417. Vancomycin aglycon: Evans, D. A.; Wood. M. R.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem., Int. Ed*. **1998**, *37*, 2700. Evans, D. A.; Dinsmore, C. J.; Watson, P. S.; Wood, M. R.; Richardson, T. I.; Trotter, B. W.; Katz, J. L. *Angew. Chem., Int. Ed*. **1998**, *37*, 2704.

(22) Reviews: Boger, D. L. *Med. Res. Rev.* **2001**, *21*, 356. Nicolaou, K. C.; Boddy, C. N. C.; Brase, S.; Winssinger, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2096. Rao, A. V. R.; Gurjar, M. K.; Reddy, K. L.; Rao, A. S. *Chem. Rev*. **1995**, *95*, 2135. Evans, D. A.; DeVries, K. M. *Drugs Pharm. Sci.* **1994**, *63*, 63.

(23) Boger, D. L.; Borzilleri, R. M.; Nukui, S.; Beresis, R. T. *J. Org. Chem.* **1997**, *62*, 4721. Boger, D. L.; Borzilleri, R. M.; Nukui, S. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 3091.

Scheme 1



easily adjusted on a biaryl precursor preceding AB macrolactamization.[19]

The EFG tripeptide **4** was anticipated to be assembled through sequential formation of the FG diaryl ether and 14-membered macrolactamization with formation of the amide bond between residues 1 and 2. Thus, the diaryl ether linkage in the 14-membered FG ring system was also expected to be introduced enlisting a phenoxide nucleophilic aromatic substitution reaction of an *o*-fluoronitroaromatic. Although this could constitute the key macrocyclization reaction used to close the FG ring system, the propensity for C_2[3] epimerization and the basic conditions required of the reaction discouraged further consideration of such an approach. Rather, we opted for an intermolecular coupling enlisting phenylglycinol derivatives incapable of base-catalyzed epimerization.

In the course of the studies, alternative preparations or improvements in the synthesis of amino acid subunits common to **2**, teicoplanin, and/or vancomycin were explored resulting in several enhancements over our earlier routes.

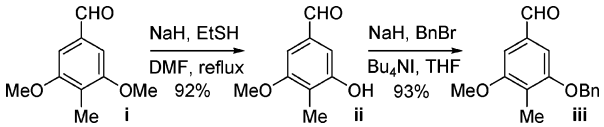
EFG Subunit 4. The precursor subunits for the three amino acid residues of the EFG tripeptide were prepared as summarized in Scheme 1. The β-hydroxy(4-fluoro-3-nitrophenyl)alanine (E ring amino acid, residue 2) is identical with the subunit found in vancomycin. Our earlier preparation[23] relied on a Schöllkopf aldol-type addition[24] (−78 °C, *n*-BuLi followed by $Sn(OTf)_2$) to 4-fluoro-3-nitrobenzaldehyde (**6**))[25] which provided high levels of diastereoselectivity for introduction of the amino acid center (C_2[2]), but was rather nonselective for the β-hydroxy center (ca. 1.2:1) necessitating a separation of the resulting diastereomers. Although we were not able to improve this diastereoselection through choice of the countercation,[26] the ease of the synthesis (two steps) and availability of the chiral reagent more than made up for the diastereoselectivity of the reaction. This was improved significantly herein using an α-hydroxypinanone chiral auxiliary in a diastereoselective anti-aldol reaction of a glycine imine (Scheme 1). Following the protocol of Solladié-Cavallo,[27] aldehyde **6** was treated with the titanium enolate derived directly from ethyl (+)-(1*R*,2*R*,5*R*)-2-hydroxypinan-3-iminoglycinate[27,28] (**5**, 2 equiv of Et_3N, 1.1 equiv of $ClTi(OEt)_3$, CH_2Cl_2, 0 °C, 16 h) to provide near exclusive (94% de) formation of the anti-aldol product **7** (75%, 94% ee), which was subsequently hydrolyzed (aqueous HCl−THF, 25 °C, 2 d, quantitative) to provide **8**.[29] Alcohol protection (3 equiv of TBSOTf, 2 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 6 h, 80%) and Teoc[30] protection of the free amine (1.5 equiv of Teoc-OBt,[31] 2.2 equiv of Et_3N, dioxane, 25 °C, 18 h, 90%) provided **10**. Hydrolysis of the ester (4 equiv of LiOH, *t*-BuOH−H_2O, 2:1, 25 °C, 18 h, 98%) completed a 5-step synthesis of **11** (54% overall) from commercially available materials.

The F and G ring phenylglycine precursors were prepared by employing complementary Sharpless asymmetric aminohydroxylation (AA) reactions.[32] The G ring precursor **13**, an (*R*)-phenylglycinol, was enlisted in our teicoplanin synthesis, and its preparation was conducted as detailed.[19,33] The F ring (*S*)-phenylglycinol **15**[17] was obtained using the complementary $(DHQ)_2PHAL$ catalyst and incorporated into the synthesis after a three-step conversion to **17**. Thus, primary alcohol protection of **15** as a MEM ether (7 equiv of MEMCl, 5 equiv of *i*-Pr_2-NEt, THF, 25 °C, 19 h, 99%) provided **16** as a white crystalline solid, and Cbz deprotection (H_2, 10% Pd/C, MeOH, 25 °C, 3 h) followed by protection of the free amine as a trifluoroacetamide (4.5 equiv of TFAA, 8 equiv of pyridine, CH_2Cl_2, 25 °C, 2 h) afforded **17** in excellent yield (96% for two steps). As such, the F ring residue was synthesized in 9 steps in 51% overall yield from commercially available 3,4,5-trimethoxybenzaldehyde.[34]

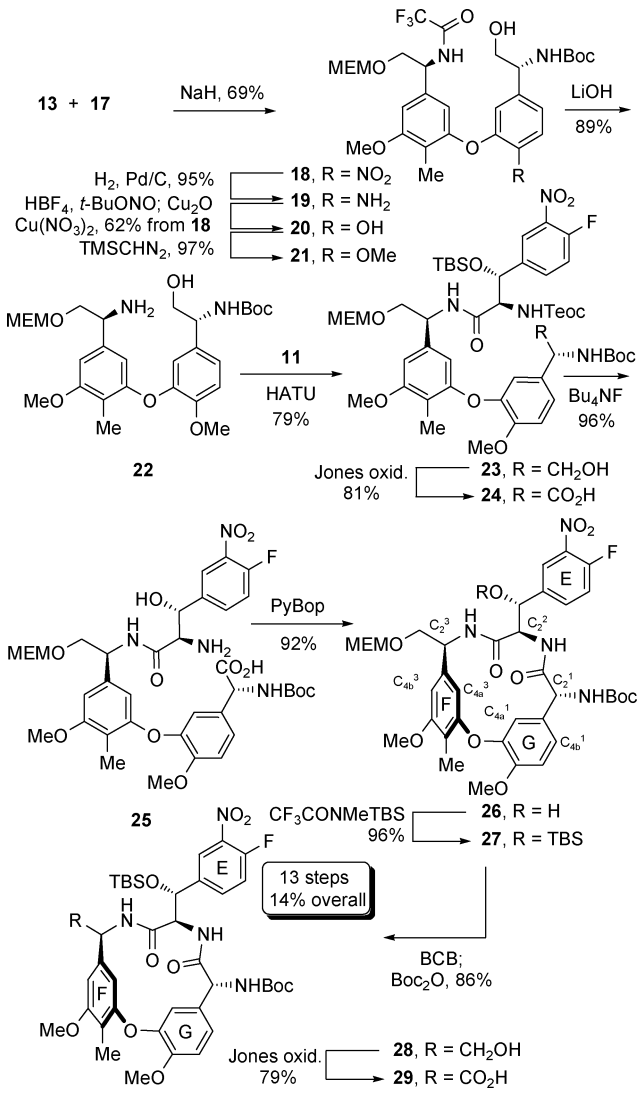
The key coupling of **13** and **17** with formation of the diaryl ether in an intermolecular phenoxide aromatic nucleophilic substitution reaction on the *o*-fluoronitroaromatic was accomplished with NaH (1.05 equiv, THF, 25 °C, 15 h) providing **18** in good yield (69%), Scheme 2. In related work on

(24) Schöllkopf, U.; Neubauer, H.-J. *Synthesis* **1982**, 864.
(25) Commercially available from Acros or prepared by nitration (HNO_3, H_2SO_4 (concentrated), 0 °C, 3 h, 80%) of the significantly less expensive 4-fluorobenzaldehyde.

(26) Schöllkopf, U.; Groth, U.; Deng, C. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 798. Schöllkopf, U.; Nozulak, J.; Groth, U. *Synthesis* **1982**, 868.
(27) Solladié-Cavallo, A.; Nsenda, T. *Tetrahedron Lett.* **1998**, *39*, 2191. Solladié-Cavallo, A.; Koessler, J. L. *J. Org. Chem.* **1994**, *59*, 9, 3240. Solladié-Cavallo, A.; Simon, M. C. *Tetrahedron Lett.* **1989**, *30*, 6011. Solladié-Cavallo, A.; Simon-Wermeister, M. C.; Schwarz, J. *Organometallics* **1993**, *12*, 3743.
(28) Yamada, S.-I.; Oguri, T.; Shiori, T. *J. Chem. Soc., Chem. Commun*. **1976**, 136.
(29) Assessment of the ee of **8** (94%) was accomplished by conversion to the corresponding *N*-Boc methyl ester and chiral phase HPLC analysis.
(30) Teoc = (2-(trimethylsilyl)ethoxy)carbonyl.
(31) Teoc-OBt = 1-[2-(trimethylsilyl)ethoxycarbonyloxy]benzotriazole: Shute, R. E.; Rich, D. H. *Synthesis* **1987**, 346.
(32) Reddy, K. L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 1207.
(33) Rao, A. V. R.; Gurjar, M. K.; Lakshmipathi, P.; Reddy, M. M.; Nagarajan, M.; Pal, S.; Sarma, B. V. N. B. S.; Tripathy, N. K. *Tetrahedron Lett.* **1997**, *38*, 7433.
(34) Prepared by Wittig reaction of **iii** (2.7 equiv of $Ph_3P{=}CH_2$, THF, −78 to 0 °C, 8 h, 91%) which was prepared from **i** (Azzena, U.; Cossu, S.; Denurra, T.; Melloni, G.; Piroddi, A. M. *Synthesis* **1990**, 313) in two steps as shown below (3 equiv of NaH, 4 equiv of EtSH, DMF, reflux, 1 h, 92%; 1.1 equiv of NaH, 1.05 equiv of BnBr, 0.1 equiv of Bu_4NI, THF, 25 °C, 8 h, 93%).



Scheme 2



teicoplanin, we had accomplished a similar transformation in DMSO with excess K_2CO_3 as the base and 18-c-6 as a coreagent. With the current substrates, these conditions gave significantly lower yields (20−30%) than those achieved with teicoplanin (70%).[18] In part, this may be attributed to the slower reaction of **17** due to the increased steric hindrance of the phenoxide resulting from the *o*-methyl substituent and the now competitive reaction of alternative, but less acidic, nucleophilic sites. Accordingly, stoichiometric use of an irreversible base deprotonation coupled with milder reaction conditions (THF vs DMSO) allowed us to conduct the transformation in yields (65−69%) essentially equivalent to those previously disclosed,[18] without resorting to primary alcohol or further amide protections. Reduction of **18** to the corresponding aniline (H_2, 10% Pd/C, MeOH, 25 °C, 1.5 h), diazotization (1.1 equiv of *t*-BuONO and HBF_4, CH_3CN, 0 °C, 10 min), and phenol introduction (45 equiv of Cu_2O, 200 equiv of $Cu(NO_3)_2$, H_2O, 0 °C, 1 h) gave **20** in 62% overall yield. Phenol *O*-methylation (6 equiv of $TMSCHN_2$, benzene−MeOH, 25 °C, 20 h, 97%) and deprotection of the trifluoroacetamide (9 equiv of LiOH, MeOH, 25 °C, 12 h, 89%) provided **22**, ready for coupling with the E ring amino acid.

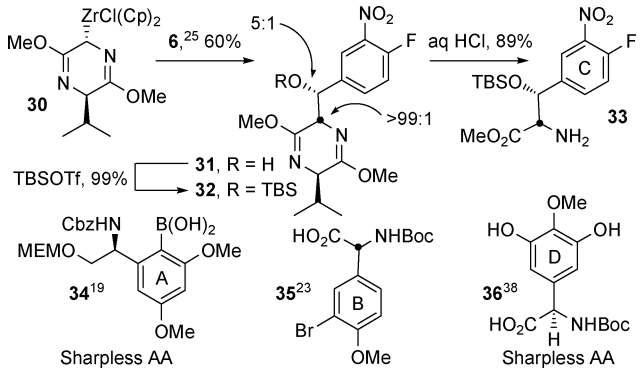
The carboxylic acid **11**, by virtue of the β-silyloxy group, was considerably slower at participating in an amide bond coupling than the corresponding teicoplanin E ring carboxylic acid. As a consequence, its coupling with **22** was more challenging than anticipated and suffered competitive C_2^2 epimerization leading to generation of variable amounts of an additional minor, but separable, diastereomer. A considerable but not exhaustive range of conditions were explored for coupling **22** with **11**, including variation of reagent (PyBop, HOAt/EDCI, HOBt/EDCI, DEPBT, and HATU),[35] temperature (−45 to 25 °C), and number of coupling reagent equivalents (1.5−5.0). Under optimized conditions, treatment of the coupling partners with HATU (4.6 equiv, 5 equiv of $NaHCO_3$, 0.04 M THF, −10 to 0 °C, 2 days) gave **23** in good yield (79%) along with a significant amount of the separable C_2^2 epimer (10−20%). Diastereoselectivity as high as 8:1 was achieved in some instances, but typically it was around 4:1. Adjusting the ratio of coupling reagent to base gave diastereoselectivities as high as 12:1, although the yield of **23** was typically lower (65%). Two-step primary alcohol oxidation (10 equiv of Dess−Martin periodinane (DMP), CH_2Cl_2, −5 °C, 3 h; 7 equiv of $NaClO_2$, resorcinol, aqueous NaH_2PO_4−DMSO−EtOAc, −5 °C, 1 h) provided **24** in disappointing yields (48%), presumably attributable to instability of the intermediate aldehyde and low recovery of the product due to its limited solubility. In contrast, single step dilute Jones oxidation of **23** (6.5 equiv of Jones reagent,[36] 0.01 M acetone, 0 °C, 2 h) gave a superior yield (73%) of **24** and was operationally much simpler to conduct, and the product was easier to isolate and purify. Removal of the Teoc protecting group (5 equiv of Bu_4NF, THF, 25 °C, 12 h, 96%) provided the amino acid **25** and set the stage for closure of the 14-membered ring. The key macrolactamization was accomplished by slow addition of **25** to a solution of PyBop (7 equiv, 7 equiv of $NaHCO_3$, 10% DMF−CH_2Cl_2, 25 °C, 5 h) to give **26** in superb yield (92%). Strong nOe's between C_2^1-H/C_{4b}^1-H, C_{4a}^1-H/C_{4a}^3-H, and C_2^3-H/C_{4b}^3-H, only a weak C_2^1-H/C_{4a}^1-H nOe, and the absence of a C_2^3-H/C_{4a}^3-H nOe established the orientation of the diaryl ether and its relationship to the backbone peptide chain as shown in Scheme 2. Protection (49 equiv of $CF_3CONMeTBS$, CH_3CN, 45 °C, 1 h, 96%) of the β-hydroxy group followed by MEM ether deprotection (10 equiv of *B*-bromocatecholborane (BCB), CH_2Cl_2, 0 °C, 2.5 h; then 2.8 equiv of Boc_2O, 0.6 equiv of $NaHCO_3$, DMF, 25 °C, 12 h, 86% for two steps) gave **28**. Single step direct oxidation of the primary alcohol to the carboxylic acid **29** (6.5 equiv of Jones reagent,[36] acetone, 0.0025 M, −10 to 0 °C, 1.5 h) completed the preparation of EFG ring system **4** (79%). Thus, the fully protected EFG ring system was assembled in 13 steps (14% overall) from the constituent amino acid precursors.

Synthesis of the Ristocetin ABCD Ring System. The ristocetin ABCD ring system is identical with that found in vancomycin and teicoplanin with the exception that it lacks the C ring aryl chloride. This simplifies the stereochemical challenges to one that only needs to control the AB ring system biaryl atropisomer stereochemistry. As such, the order of ring closures (CD followed by AB ring closure) and method for

(35) Abbreviations: PyBop = benzotriazol-1-yl-oxytrispyrrolidinophosphonium hexafluorophosphate; HATU = 2-(1*H*-7-azabenzotriazol)-1-yl-1,1,3,3-tetramethyluronium hexafluorophosphate; Bop = (1-benzotriazolyloxy)-tris(dimethylamino)phosphonium hexafluoride; EDCI = 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide; HOBt = 1-hydroxybenzotriazole; HOAt = 1-hydroxy-7-azabenzotriazole.

(36) Prepared by treating CrO_3 (100 mg, 1 mmol) with H_2SO_4 (100 μL) in H_2O (320 μL) to give a 2.38 M solution.

Scheme 3

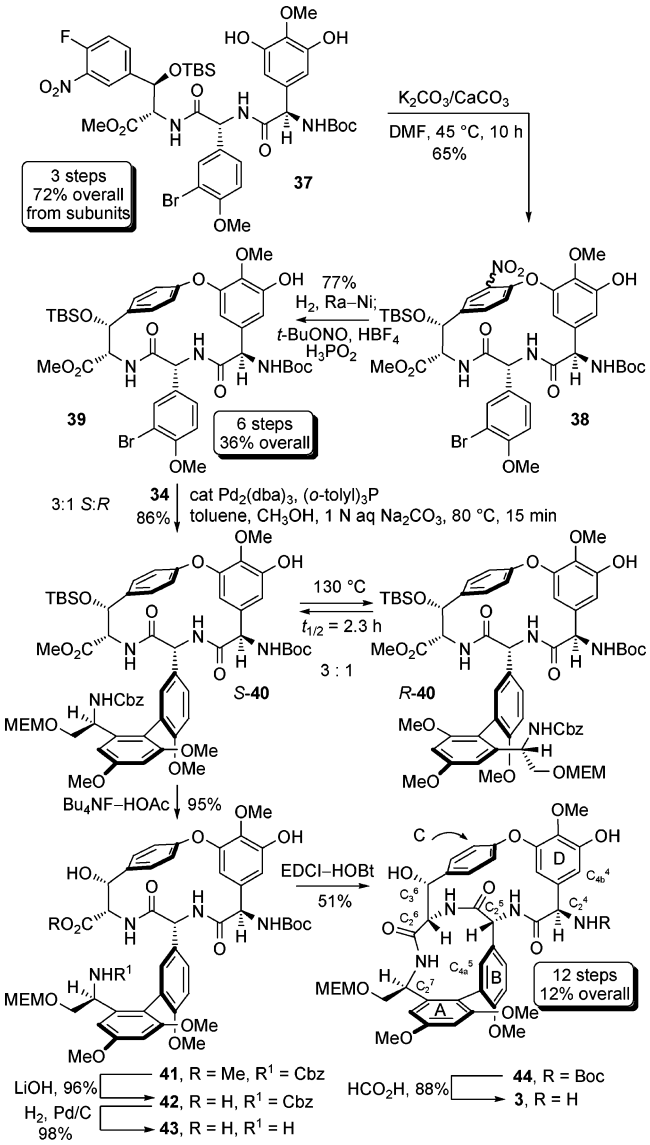


introducing and adjusting the AB biaryl atropisomer stereochemistry that we devised for the preparation of the vancomycin and teicoplanin ABCD ring system,[19] which differs from that found in either the Nicolaou or Evans approaches,[20,21] is perfectly suited for the challenges posed by **2**.

The individual amino acid subunits for **3** were prepared largely by the approaches detailed earlier for vancomycin[19] with two notable improvements, Scheme 3. The C ring β-hydroxy-(4-fluoro-3-nitrophenyl)alanine **33** was prepared by enlisting a Schöllkopf aldol-type addition[37] of the transmetalated Zr anion with **6**[25] affording **31** with superb control of the α-amino acid stereochemistry (≥99:1) and good levels of diastereoselectivity for introduction of the β-hydroxy (C_3[6]) center (5:1) as described in our earlier work.[23] However, hydrolysis of **31** with removal of the Schöllkopf auxiliary to provide the β-hydroxy amino acid ester was occasionally problematic, leading to partial hydrolysis and piperazinedione formation. We found that this variability in the hydrolysis could be avoided by simply reversing the order of steps for the preparation of **33**. Thus, TBS ether protection of **31** (4 equiv of TBSOTf, 4.5 equiv of 2,6-lutidine, CH_2Cl_2, 25 °C, 3 h, 99%) followed by hydrolysis (0.25 N HCl, THF−CH_3CN, 2:1, 25 °C, 18 h, 89%) of the Schöllkopf auxiliary provided **33** cleanly and dependably without complications arising from partial hydrolysis. Additionally, a large scale, single pot procedure (4 equiv of MeI, 2.5 of equiv Li_2CO_3, DMF, 70 °C, 18 h, followed by 4 equiv of BnBr, 4 equiv of K_2CO_3, DMF, 70 °C, 18 h, 60%)[38] for the conversion of commercially available methyl 3,4,5-trihydroxybenzoate to methyl 3,5-(dibenzyloxy)-4-methoxybenzoate[23] was developed that only requires a simple recrystallization purification, shortening and simplifying the preparation of the central D ring amino acid **36**.

The tripeptide **37** was assembled from the amino acid subunits **33**−**36** in three steps (72% overall) as previously described.[23] Intramolecular S_NAr ring closure with formation of the linking diaryl ether proceeded effectively (5 equiv of K_2CO_3, 10 equiv of $CaCO_3$, 4 Å MS, DMF, 45 °C, 10 h, 65%) providing **38** as a 1.2:1 mixture of *P*:*M* atropisomers, Scheme 4. Notably, the inclusion of $CaCO_3$ in the reaction mixture serves to scavenge the released fluoride such that the TBS ether is not competitively deprotected under the reaction conditions. Removal of the activating nitro group (H_2, Raney Ni, MeOH, −10 °C, 20 min; then 1.1 equiv of *t*-BuONO and HBF_4, CH_3CN, 0 °C, 10 min, followed by addition to aqueous H_3PO_2 containing Cu_2O) gave

Scheme 4

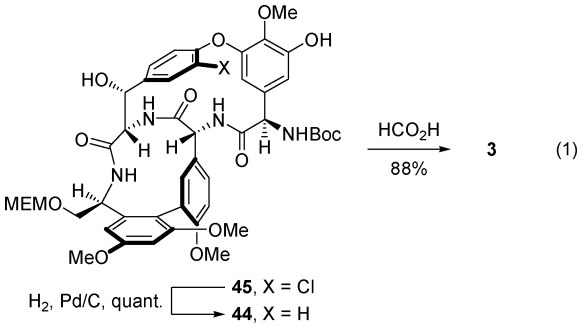


39 in good yield (77%) as a single compound, completing the synthesis of the CD ring system (6 steps, 34% overall). Suzuki biaryl coupling of **39** with the boronic acid **34**[19] furnished **40** in superb yield (86%) and satisfactory diastereoselection (2−3:1, *S*:*R*). Interestingly, this atropselectivity varied from 1:1 to 3:1 depending on the reaction conditions (time at 80 °C) and most likely represents a nonselective Suzuki coupling followed by in situ thermal atropisomer equilibration to provide the thermodynamically controlled 3:1 mixture favoring the natural atropisomer stereochemistry. Notably, the Suzuki coupling of the hindered, electron-rich aryl bromide proceeds uniquely well under these conditions (80 °C, 15 min, 86%) and benefits from carefully chosen features that accelerate the typically slow Pd(0) insertion into the aryl bromide (0.3 equiv of $Pd_2(dba)_3$, 1.5 equiv of $(o\text{-tol})_3P$, 10:3:1 toluene−CH_3OH−1 N aqueous Na_2CO_3) avoiding competitive degradation of the sensitive aryl boronic acid. The unnatural biaryl atropisomer stereochemistry of isolated (*R*)-**40** was adjusted by thermal equilibration (*o*-dichlorobenzene, 130 °C, 13 h, $t_{1/2}$ = 2.3 h) providing a 3:1 mixture of separable (*S*)-**40**:(*R*)-**40**. All the minor unnatural atropisomer could be recycled into (*S*)-**40** required for the synthesis using this procedure. Silyl ether deprotection (4.6 equiv

(37) Schöllkopf, U.; Nozulak, J.; Grauert, M. *Synthesis* **1985**, 55.
(38) Experimental details can be provided upon request. Boger, D. L.; Borzilleri, R. M.; Nukui, S. *J. Org. Chem.* **1996**, *61*, 3561.

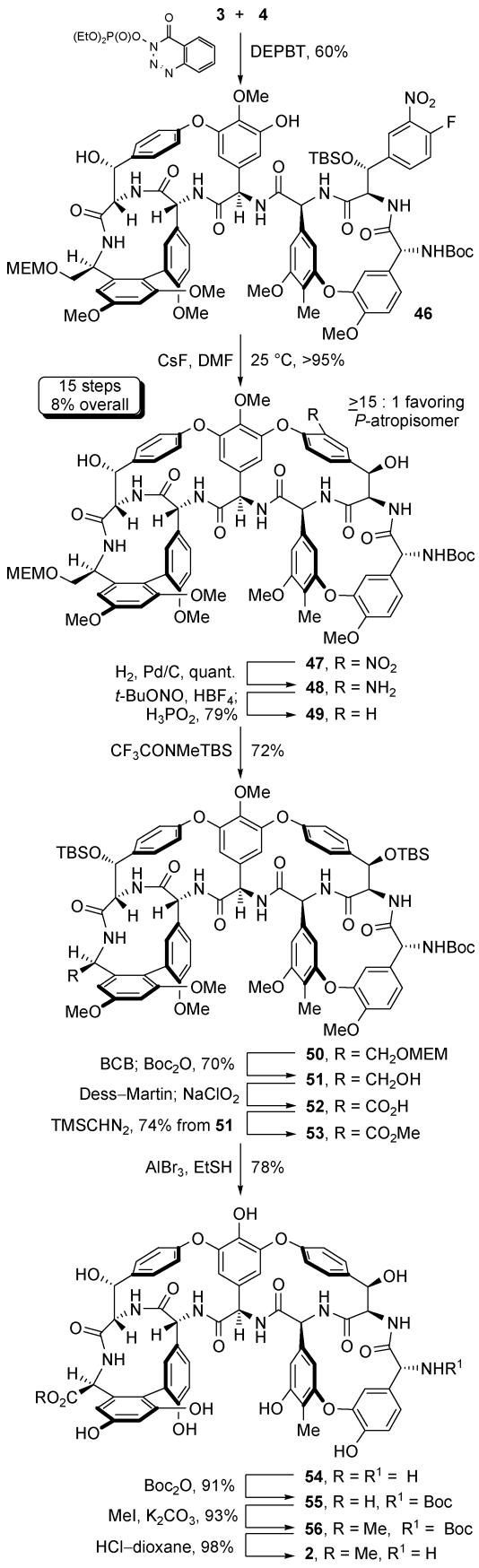
of Bu_4NF, 5.4 equiv of HOAc, THF, 25 °C, 10 h, 95%), hydrolysis of the methyl ester (2 equiv of LiOH, THF, 0 °C, 2 h), and Cbz hydrogenolysis (H_2, 10% Pd/C, 2.5:1 EtOAc−EtOH, 25 °C, 7.5 h) gave amino acid **43** setting the stage for ring closure to form the 12-membered AB macrocycle. To accomplish the macrolactamization, **43** was subjected to treatment with EDCI−HOBt (5 equiv each, 5:1 CH_2Cl_2−DMF, 0.002 M, 0 °C, 16 h) to provide **44** in good yield (51%). *N*-Boc deprotection of **44** under conditions that do not affect the MEM ether (HCO_2H−$CHCl_3$, 25 °C, 7 h, 88%) yielded **3**, the ristocetin ABCD ring system (12 steps, 12% overall).

Intermediates **44** and **3** proved identical in all respects with authentic samples prepared by hydrogenolysis of the aryl chloride found in our vancomycin precursor **45**,[19] constituting its ABCD ring system. Thus, **45** was reduced (H_2, 10% Pd/C, MeOH, 25 °C, 40 psi, 12 h, quantitative) and *N*-Boc deprotected (HCO_2H−$CHCl_3$, 25 °C, 7 h, 88%) to give an authentic sample of **44** and **3** (eq 1).



Coupling of 3 and 4 and Completion of the Synthesis. With the EFG and ABCD ring systems in hand, attention was directed toward completing the synthesis, beginning with the coupling of **3** and **4**, Scheme 5. The transformation was accomplished by following a key protocol developed in the course of our synthesis of the teicoplanin aglycon[18] (2.5 equiv of DEPBT,[39] THF, −5 to 0 °C, 5 h, 60%) to furnish **46** in good yield. In line with observations first divulged in these efforts, the DEPBT-mediated coupling reaction uniquely proceeded with little or no epimerization that plagued alternative reagents to provide **46** in excellent diastereoselectivity (>10:1). Closure of the remaining DE ring system was accomplished by a S_NAr reaction initiated by treating **46** with CsF (100 equiv, DMF, 0.006 M, 25 °C, 8 h, ≥95%) to provide **47**, constituting the complete ristocetin aglycon carbon skeleton, in exceptional yield and excellent atropdiastereoselectivity (≥15:1). Remarkably, the reaction proceeds very effectively at room temperature even in DMF (vs DMSO) with no perceptible epimerization of the sensitive $C_2{}^3$ center. The cyclization presumably benefits from preorganization of the substrate since the ring closure of **46** proceeds much more readily than that of analogous substrates that lack the preformed ristocetin FG ring system.[18,40] Such substrates fail to close effectively in DMF and typically require harsher reaction conditions, higher reaction temperatures, and DMSO (vs DMF) for observation of reaction at 25 °C. Removal of the activating nitro group (H_2, 10% Pd/C, EtOAc, 25 °C, 2 h; then 1.1 equiv of *t*-BuONO and HBF_4, CH_3CN, 0 °C, 10 min, followed by addition to aqueous H_3PO_2, 0 °C, 1 h, 79%)

Scheme 5



(39) Fan, C.-X.; Hao, X.-L.; Ye, Y.-H. *Synth. Commun.* **1996**, *26*, 1455. Li, H.; Jiang, X.; Ye, Y.-H.; Fan, C.; Romoff, T.; Goodman, M. *Org. Lett.* **1999**, *1*, 91. DEPBT = 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one.

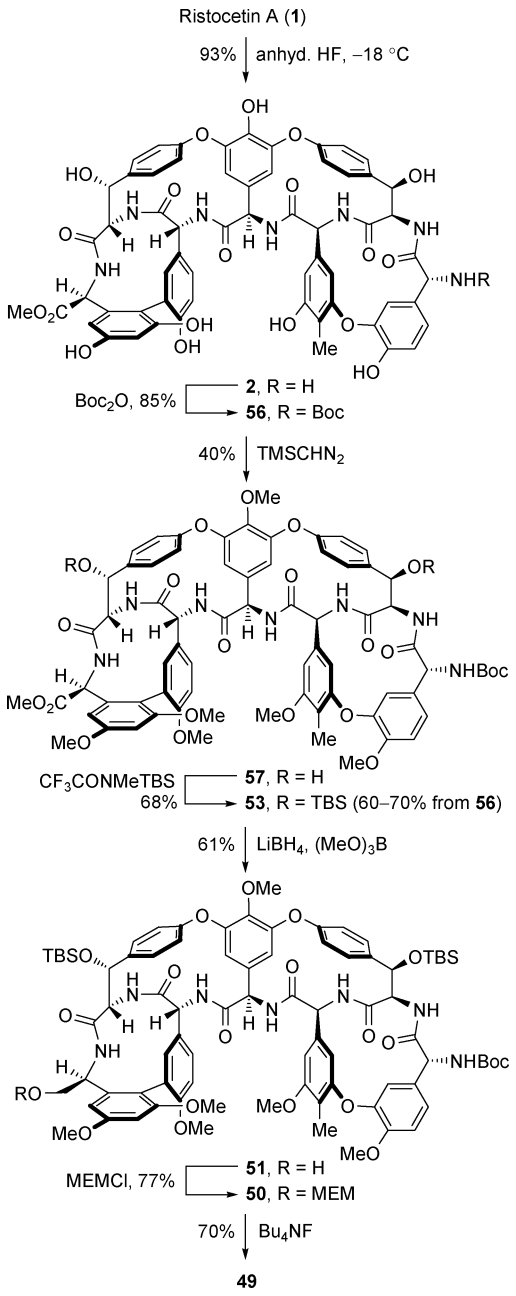
(40) Mori, Y.; McAtee, J. J.; Rogel, O.; Boger, D. L. *Tetrahedron Lett.* **2001**, *42*, 6061.

provided **49** in a three-step sequence that was typically accomplished without purification of the sensitive intermediate aniline.

With the protected aglycon in hand, the synthesis was completed through a series of functional group manipulations. The first task was to oxidize the residue 7 C-terminus to the corresponding carboxylic acid. Silyl ether protection (160 equiv of $(CF_3CONMe)TBS$, CH_3CN, 25 to 50 °C, 5 days, 72%) of the C_3^2 and C_3^6 secondary alcohols provided **50**, and subsequent removal of the MEM ether (15 equiv of BCB, CH_2Cl_2, 0 °C, 4 h; then 2.8 equiv of Boc_2O, $NaHCO_3$, THF, 25 °C, 2 h, 70% for two steps) afforded alcohol **51**. Two-step Dess−Martin/$NaClO_2$ oxidation of **51** (14 equiv of DMP, CH_2Cl_2, 25 °C, 9 h; then 15 equiv of $NaClO_2$, resorcinol, aqueous NaH_2PO_4−DMSO, 25 °C, 1 h) provided carboxylic acid **52**, which was converted to the methyl ester **53** (120 equiv of $TMSCHN_2$, benzene−MeOH, 25 °C, 1 h, 74% for two steps) for ease of purification. Global deprotection (178 equiv of $AlBr_3$, EtSH, 25 °C, 3 h, 78%) provided **54** cleanly in a reaction that served to remove the six methyl ethers, the C-terminus methyl ester, two TBS ethers, and the N-terminus Boc group (10 protecting groups!). Completion of the synthesis simply required formation of the C-terminus methyl ester, which was best conducted using the three-step sequence of N-terminus Boc protection (11 equiv of Boc_2O, 13.5 equiv of $NaHCO_3$, dioxane−H_2O, 25 °C, 4 h, 91%), methyl ester formation (15 equiv of CH_3I, 14 equiv of $NaHCO_3$, DMF, 25 °C, 8 h, 93%) under conditions that do not suffer from competitive phenol *O*-methylation, and final *N*-Boc deprotection (4 M HCl−dioxane, 25 °C, 5 h, 98%) to provide the ristocetin aglycon identical in all respects with authentic material.

Ristocetin Degradation: Preparation of a Correlation Sample of 49. Preceding our efforts, the ristocetin aglycon had been obtained in two sequential deglycosylation steps (5% HCl−MeOH, reflux, 1.25 h; Et_3SiH, TFA, 65 °C, 5.5 h) and suffered from very low conversions (8% overall) and a tedious chromatographic purification.[14,41,42] Thus, we examined a variety of alternatives and established that anhydrous HF (−18 °C, 1−1.5 h, 93%) or HF/pyridine (25 °C, 2 h, 60%) treatment of ristocetin A (**1**) provided a very effective, single-step deglycosidation procedure affording pure **2** after a simple trituration (EtOAc, 3×) to remove the released carbohydrate byproducts.[43] *N*-Boc formation to provide **56** proceeded without difficulty provided the reaction was conducted at 0 °C for no longer than 2 h, Scheme 6. Prolonged reaction times or higher reaction temperatures resulted in incorporation of additional Boc protecting groups in the molecule. Exhaustive methylation of the six phenols was best accomplished by treatment of **56** with excess $TMSCHN_2$ (100 equiv, benzene−MeOH, 25 °C, 7 h) providing **57** in conversions that were more satisfactory than treatment of **56** with K_2CO_3−MeI under a range of conditions (34%). The bis *O*-silylation of **57** using $(CF_3CONMe)TBS$ (CH_3CN, 48 °C, 5 d) provided **53** in conversions as high as 70%, and a corresponding mono TBS ether presumably resulting from selective C_3^6 alcohol protection could also be isolated (31−25%). Typically, the conversion of **56** to **53** provided more material and proceeded in higher overall conversions (60−70%) without an intermediate purification of **57**. Reduction of the C-terminus methyl ester ($LiBH_4$, $(MeO)_3B$, THF, 25 °C, 30 h, 61%), conversion of the primary alcohol **51** to the MEM ether (MEMCl, *i*-Pr_2NEt, CH_2Cl_2, 25 °C, 7 h, 77%), and TBS ether deprotection (Bu_4NF, THF, 25 °C, 2 h, 70%) provided authentic **49** identical in all respects with synthetic material prepared herein.

Scheme 6



Conclusions. The first total synthesis of the ristocetin aglycon was achieved through implementation of a modular and convergent strategy developed for the synthesis of the glycopeptide antibiotics. A very effective 12-step synthesis of the ABCD ring system **3** from its constituent amino acid subunits sequentially features an intramolecular aromatic nucleophilic substitution reaction for formation of the diaryl ether and closure of the 16-membered ring system, a respectively diastereoselective (3:1, 86%) Suzuki coupling for installation of the AB biaryl

(41) Rajananda, V.; Norris, A. F.; Williams, D. H. *J. Chem. Soc. Pak.* **1979**, *1*, 29.
(42) Herrin, T. R.; Thomas, A. M.; Perun, T. J.; Mao, J. C.; Fesik, S. W. *J. Med. Chem.* **1985**, *28*, 1371.
(43) Wanner, J.; Tang, D.; McComas, C. C.; Crowley, B. M.; Jiang, W.; Boger, D. L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1169.

linkage, and an effective macrolactamization (51%) for closure of the 12-membered AB ring system. Notably, the diastereoselectivity of the initial S_NAr closure of the CD ring system is not crucial for ristocetin (activating nitro group is removed), and a thermodynamic equilibration of the AB biaryl atropisomers, which favors the natural stereochemistry (3:1, *S*:*R*) could be used to adjust the atropisomer stereochemistry and recycle all of the unnatural atropisomer into the synthesis.

A similarly effective 13-step synthesis of the 14-membered EFG ring system **4** was implemented by enlisting a room-temperature intermolecular S_NAr reaction for formation of the linking FG diaryl ether (69%) and a key macrolactamization reaction (92%) of the $C_1^1-N_2^2$ amide to close the 14-membered EFG ring system. Enroute to the key fragments, significant improvements in the preparation of the amino acid subunits common to the entire class of glycopeptide antibiotics were explored and introduced (residues 2, 4, and 6).

The two key subunits **3** and **4** representing the fully functionalized ristocetin ABCD and EFG ring systems were coupled and the remaining 16-membered DE ring system was closed via formation of the diaryl ether to provide the natural product tetracyclic ring system enlisting an unusually facile (25 °C, 8 h, DMF, ≥95%) and diastereoselective (≥15:1) aromatic nucleophilic substitution reaction of a *o*-fluoronitroaromatic that benefits from preorganization of substrate.

The approach is sufficiently modular, convergent, and efficient that it should prove applicable in the synthesis of structural analogues of the glycopeptide antibiotic family required to address questions regarding bacterial resistance and target binding affinity and selectivity.

Acknowledgment. We gratefully acknowledge the financial support of the National Institutes of Health (Grant CA41101) and the Skaggs Institute for Chemical Biology and the sabbatical leave of Y.M. (Mitsubishi-Tokyo Pharmaceuticals, Inc., 1999−2001). B.M.C is a Fletcher Jones Foundation Fellow and a Skaggs Fellow. We also wish to thank Drs. J. J. McAtee and O. Rogel for the large scale supply of many of the subunit precursors (B−E) and Abbott Laboratories and Advanced Separation Technologies for the generous donation of a supply of the natural product.

Supporting Information Available: Full experimental details and complete characterization of all intermediates (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA039795A